Potential impact of helicobacter pylori infection on reflux disease sequence: illuminating the gap

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Potential Impact of *Helicobacter pylori* Infection on Reflux Disease Sequence

Illuminating the Gap

To the Editor:

Sonnenberg et al[1] reported striking variations in the ethnic distributions of gastroesophageal reflux disease (GERD) and Barrett esophagus (BE). Both diseases were associated with a lower prevalence of *Helicobacter pylori* infection (*Hp*-I) than the control population, though its prevalence in GERD and BE was higher in male than female patients, thereby running contrary to a simple consideration of an inverse relationship between *Hp-I* and these diseases.[1]

In this regard, we recently suggested that epidemiological studies regarding *Hp*-I, GERD and BE-related esophageal adenocarcinoma (EAC) underestimated potential co-factors of EAC development.[2] Furthermore, large-scale studies concluded against the protective role of *Hp* to GERD.[2] The current worldwide *Hp*-I prevalence is about 58% (varied from 39.9% to 84.2%)[3]; its current prevalence in Asia is 66.6%. In contrast, the current global prevalence of GERD varies from 2.5% to 51.2%; its range in Asia is 33% compared with 28% of the western countries.[3] This means that the conventional claim that declining *Hp* prevalence has led to a rise in GERD and its complications BE and EAC[3,4] needs to be carefully studied. For instance, a large-scale study (~21,000 cases) reported that the decline in *Hp*-I parallels the reduction in peptic ulcer prevalence, and that the rise in GERD and/or reappearance of GERD following *Hp* therapy is rare[2]; contrary to expectations, patients hospitalized with duodenal ulcers (~61,500 cases), obviously attributed to *Hp*-I, had a 70% increased risk of EAC[5]; Malaysians, who for a long time have had a low prevalence of *Hp*-I, also show a low incidence of GERD, BE and distal esophageal cancers, signifying that *Hp*-I is not protective against these pathologies and its absence may be beneficial[6]; in a predominantly Caucasian population with a high prevalence of *Hp* gastritis, *Hp*-I was not inversely connected with BE (neither presence of erosive esophagitis, length of BE nor dysplasia was associated with the presence of *Hp*-I)[7]; 2 additional studies showed that *Hp* eradication leads to better control of GERD symptoms and improves esophagitis.[8,9] Moreover, other authors, previous supporters of the hypothesis that *Hp* "protects" against GERD, relented, claiming that *Hp* therapy does not cause or protect against GERD, and recommending *Hp* eradication in GERD.[10] Such data further potentiate the consideration that *Hp* is not "protective" against anything, including GERD[11] and its complications BE and EAC.

Likewise, the hypothesis that increased acidity, after *Hp*-I eradication, could trigger GERD-BE-EAC sequence warrants careful reconsideration. Contrariwise, transient lower esophageal sphincter (LES) relaxations consist the substantial component of esophageal injury[3] and *Hp*-I disables normal LES, probably by nitric oxide intermittent overproduction and nonselective relaxation of smooth muscles. In addition, *Hp*-I influences the gastrointestinal microbiota composition including the presence of gastric species such as *Campylobacter*; *Hp*-I induced atrophy impairs the chemical defense of stomach, thus promoting the gastric microbiota dysbiosis which might contribute to BE-EAC sequence as etc implied by the high concentrations of *Campylobacter* species in BE biofilm and the predominance of gram-negative bacteria.[3] Moreover, *Hp* could directly hurt the esophagus and induce prostaglandins (PGs) overproduction that relax LES.[2] At molecular level, *Hp*-I induces, oncogenic gastrin and other molecular alterations which contribute to BE malignant progression.[2,3] Specifically, *Hp*-I induced oncogenic gastrin, which, concerning its essential role in oncogenic progression in BE, stimulates proliferation via Janus Kinase (JAK) 2 and Akt-dependent nuclear factor-kappa B (NF-κB) activation in Barrett's EAC cells, exhibits an anti-apoptotic effect via Bcl-2 protein and survivin upregulations, and provokes the mitogenic and carcinogenic cyclooxygenase (COX)-2 expression. Moreover, *Hp* activates the mentioned NF-κB, a transcription regulator of inflammatory genes, including COX-2 that regulates gastrointestinal malignant cell growth and proliferation. PGs originated from upregulated COX-2 are involved in BE malignant progression, by perpetuating chronic inflammation and the mitogenic and anti-apoptotic actions of PGs are mediated via activation of many aforementioned signaling pathways including NF-κB, Src, JAK2/STAT3, ERK, MAPK and PI3K/Akt kinases. In addition, *Hp*-I could trigger specific molecular alterations (genetic instability, E-cadherin methylation, monoclonal antibody Das-1) connected with BE pathophysiology, and stimulated Ki-67 expression predicting neoplasting progression in BE.[3] Furthermore, *Hp*-related metabolic syndrome appears to contribute to the pathophysiology of GERD-BE-EAC sequence,[12,13] and thus further research is needed to clarify this topic.

A final dilemma arises: Which cancer do we prefer to deal with, gastric cancer or EAC? The plethora of agents contributing to EAC does not allow to simplify its pathogenesis and thus the *Hp*-I positive association with gastric cancer, duodenal cancer, and colorectal cancer[12,14] but negative association with EAC appears inconsistent, thereby warranting further investigation.

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The authors declare that they have nothing to disclose.
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